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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Holl et al.

Group: 1743

Serial No. 09/688,055

Examiner: Unassigned

Filed: October 13, 2000

For: LIQUID ANALYSIS CARTRIDGE

CERTIFICATE OF MAILING

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PETITION FOR ADVANCED EXAMINATION

Commissioner for Patents
Washington, D.C. 20231

Sir:

The applicant respectfully submits the following petition for advanced examination under 37CFR 1.102.

- All claims are directed to a single invention. (See the attached Preliminary Amendment.)
- A preexamination search was conducted as set forth below.
- A detailed discussion of the references pointing out how the claimed subject matter is patentable over the references is set forth below.
- A copy of each of the references discussed is enclosed.
- A check for the Petition fee in the amount of $130 is enclosed.

Preexamination Search

We hereby submit claims 172-220 as directed to a single invention and patentable over the prior art. In addition to the references listed on form PTO-1449 of the parent application, as signed by Examiner Bex, and those cited by the examiner in the parent application, we have included the results of a pre-examination patent search conducted by Washington Patent Services well as the results of the international search report for the PCT application corresponding to the present application.

The search by Washington Patent Services was conducted in U.S. Patent classes/subclasses 204/604, 603and 436/518, 52. Foreign publications were also searched.

The international search for the corresponding PCT Application, Serial No. PCT/US99/09322, was conducted in the United States in U.S. Patent classes and subclasses: US 422/58, 68.1, 81,100, 82.05, 82.08, 104; 436/43, 164, 165, 172, 174, 179, 180.

One copy of each of the references found in these searches is enclosed with this petition, as well as a copy of each reference cited in parent application Serial No. 09/080,691 by the Examiner. These references were listed on the PTO-1449 forms filed with the Information Disclosure Statement filed in this application on January 16, 2001. The remaining references listed on the PTO Forms 1449 filed in the parent application were initialed but not cited by the Examiner in that application. Therefore they are not deemed relevant to patentability and are not discussed herein.

The following section discusses the patentability of the claims in view of the references identified in the preexamination search. These include:

Nordman (US 6,176,991)

Woudenberg et al. (US 6,124,138)

Moles (US 6,073,482)

Dubrow et al. (US 6,153,073)

Weigl et al. (US 6,171,865)

Li et al. (US 6,027,627)

Kaltenbach et al. (US 6,033,628)

Kennedy (WO 99/29497)

In addition, references cited in the corresponding PCT application as the result of an international search are included. These are:

Kricka, et al. (US 5,744,366)	category Y
Deoms, et al. (US 5,500,187)	category Y
Mochida (US 5,147,607)	category Y
Altendorf et al. (US 5,726,751)	category Y
Zanzucchi et al. (US 5,755,942)	category Y, P
Boyd et al. (US 5,919,711)	category A, E
Southgate et al. (US 5,863,502)	category A, P

In addition, references cited by the Examiner in the parent application as relevant to patentability are discussed below. These are:

Bormann et al. (US 5,601,727)

Chemelli (US 5,288,463)

Miyake et al. (US 5,736,100)

Weigl et al. (WO 97/39338).

Discussion of the References

To anticipate a claim, a single reference must contain each and every element of the claim either expressly or inherently. The enclosed references are therefore analyzed for disclosure of each and every element of the current claims. The current application contains independent claims 172 and 213 Claims 173-212 and 214-220 are dependent on claims 172 and 213 and therefore also contain each and every element of 172 and 213.

Nordman (US 6,176,991) describes the use of serpentine microchannels having asymmetric bends to correct for band distortion as separated fluid samples pass around bends in the microchannels. However, Nordman does not disclose several of the elements found in the current claims, including:

Sample inlet, inlet shut-off interface and storage channel: Nordman does not provide for a sample inlet or inlet shut-off interface as found in the current application. Nordman does describe reservoirs where samples and buffers may be loaded, but these reservoirs are not storage channels as taught in the present application because they are wells and not flow channels. Further, because Nordman lacks an inlet shut-off interface and any other valve downstream of his described separation channel, the separation channel of Nordman could not be used as a storage channel.

First analysis channel: Nordman does not provide for any analysis of the separated sample. None of the regions of the separation channel are described as having access to detection means.

Because of the lack of these elements, Nordman does not anticipate the claims of the present invention.

Woudenberg, et. al (US 6,124,138) is related to a device that:

> ...includes a substrate which defines a sample-distribution network having (i) a sample inlet, (ii) one or more detection chambers, and (iii) channel means providing a dead-end fluid connection between each of the chambers and the inlet. (Column 2, Line 36.)

Woudenberg further describes the use of analyte specific reagents in the detection chambers to capture the analyte of interest (column 2, line 49) optional vacuum ports to allow removal of liquid from the detection chambers, or to isolate the detection chambers from one another.

Woudenberg et al. differs from present claims 172 and 213 in that it is lacking disclosure of the following elements of these claims:

Convoluted channels: Channels of Woudenberg et al. are used solely for delivering fluid to the detection chambers and are bent only as necessary to circumnavigate other features on the device or for delivery of the sample to a plurality of detection chambers. Further, there are no **particle capture regions** in the channels of Woudenberg.

Woudenberg et al. does not anticipate the claims of this invention because it does not teach each and every element of the claims.

Moles (US 6,073,482) is directed to:

...a fluid flow module that allows for analyte sample flow therethrough while providing a site for the location of a sensing element or elements therein to detect analyte presence and/or concentration. (Abstract)

Moles describes a network of communicating microfluidic flow channels throughout multiple layers of a laminated structure that include an inlet channel comprised of multiple sample/reagent feed channels, valving to open or block flow between channels, an analysis region and detection means, and a sample outlet.

The disclosure of Moles differs from present claims 172 and 213 in that it is lacking the following elements of these claims:

Convoluted channels: The channels of Moles are used solely for delivering fluid to the analysis region and deviate from linear only where necessary to accommodate the particular valve type described in the patent, to accommodate the joining of several channels or to access the outlet. The channels of Moles, therefore, lack a **plurality of particle capture regions.**

Because of the lack of convoluted channels having particle capture regions, the invention of Moles does not anticipate the claims of this invention.

Dubrow et al. (US 6,153,073) describes microfluidic devices with improved channel and reservoir geometries as well as methods for their use. In general, the device of the described invention provides an analysis channel and load channels, reagent, sample, load and waste reservoirs, and a motive force,

such as a pump, pressure or electrophoretic means, to move the sample through an analysis channel.

Dubrow differs from present claims 172 and 213 in that it does not describe several elements of these claims, including:

sample inlet and inlet shutoff interface
first analytical valve interface
storage channel

The sample reservoirs described in Dubrow are not equivalent to the storage channel in the present invention because they are wells, not flow channels.

Convoluted channels: Dubrow et al. describes generally elongated channels for separation. The channels described are bent only to maintain equal distances between different reservoirs and the sample channel. Further, there are no **particle capture regions** in Dubrow as described and claimed in the present application.

Because of its lack of these elements, Dubrow et al. does not anticipate the claims of the present invention.

Weigl et al. (US 6,171,865) describes a reference sensor:

> ...for detecting the presence and/or measuring the concentration of analyte particles in a sample stream. The system includes: a) a laminar flow channel; b) three or more inlet means in fluid connection with the laminar

> flow channel for respectively conducting into the laminar flow channel (1) an indicator stream which may include an indicator substance which indicates the presence of the analyte particles (2) the sample stream, and (3) a reference stream, which can be a control stream and/or internal standard stream; and c) wherein the laminar flow channel has a depth and/or width sufficiently small to allow laminar flow of said streams and a length sufficient to allow particles of the analyte to diffuse into the indicator stream to form a detection area. (Abstract)

Weigl et al. further describes the use of syringes for introducing and moving fluids through the three inlets.

Weigl et al. differs from present claims 172 and 213 in that it does not disclose the following elements of these claims:

> **Storage channel**: Weigl et al. does not describe a valve at the microchannel outlet. Without a valve, the laminar flow channel described by Weigl would be unable to store fluids and is therefore differentiated from the storage channel of this invention. Further, the laminar flow microchannel described by Weigl et al. is linear and therefore does not provide **convoluted channels with particle capture regions** as claimed in the present invention.

Because Weigl et al. does not disclose these elements, it does not anticipate the claims of the present invention.

Li et al. (US 6,027,627) describes an automated electrophoretic system having a plurality of capillary tubes arranged to interface with standard microtitre plates. The macroscale system described by Li et al. includes sample inlets and

outlets, valves for the introduction of regenerating/cleaning fluids, and an analysis region. However, Li et al differs from present claims 172 and 213 in that it is lacking disclosure of:

> **convoluted storage channels having a plurality of particle capture regions.**

Because of the lack of these elements, Li et al. does not anticipate the claims of the present invention.

Kaltenbach et al. (US 6,033,628) "...relates to a miniaturized planar column device for use in a liquid phase separation apparatus." (Column 2, line 49.) The patent describes a device having sample inlets and outlets, microchannels for separation in fluid connection with the inlets and outlets, a sample plug (holding chamber for sample to be analyzed), reservoirs for buffers and reagents, microvalves and micropumps for delivering the buffers and reagents to the separation channel, and a portion of the separation channel for access to detection means. The microchannels may be of any configuration including serpentine and spiral (column 11 line 9).

Kaltenbach et al. differs from present claims 172 and 213 in that it does not disclose other elements of these claims, including: **valve interface between channel and analytical region** Kaltenbach has only a valve external to the inlet and no valve downstream of the inlet. This prevents using the device of Kaltenbach as a storage chamber, therefore Kaltenbach also lacks a **storage channel**.

valve too downstream from inlet

Because of the lack of valve interfaces and a storage channel, Kaltenbach et al. does not anticipate the claims of this invention.

Kennedy (WO 99/29497) discloses methods for making microfluidic channels between sheets of laminate using printing techniques. These channels may have intricate shapes and geometries because of the printing methods used.

Kennedy differs from present claims 172 and 213 in that it is lacking disclosure of elements of these claims, including:

sample inlet

valves

storage channel: Because of a lack of valves in Kennedy, it would be impossible for the channels of Kennedy to be used as storage channels.

analysis region/access to detection means

Because of the lack of these elements, Kennedy does not anticipate the claims of the present invention.

Kricka et al. (US 5,744,366) describes mesoscale devices and methods for the analysis of motile cells. Generally:

> ... The devices feature a solid substrate microfabricated to define a flow system including one or more ports or chambers, connected to elongate channels of various shapes having a mesoscale cross-sectional dimension on the order of 0.1 μm to 1000 μm.... (Abstract)

The substrate described by Kricka et al. includes a transparent cover for optical probing, an inlet (that may be sealed) and receiving well, an elongated

channel that may be either straight, tortuous or serpentine, an optional filter at the inlet, optional outlet ports (that may be sealed), a detection region, a pump for liquid delivery and optional thermal regulating systems.

Kricka et al. differs from present claims 172 and 213 in that it is lacking disclosure of:

a first analytical valve interface between a storage channel and an analytical region.

Because Kricka et al. does not teach each and every element of the current claims, it does not anticipate the current claims.

Deoms et al. (US 5,500,187) generally describes an assay device for analyte detection. Specifically, it describes an optical agglutination assay device and method for its use. The device of Deoms et al. has reagent reservoirs in fluidic connection to a sample track (channel), an entry port for receiving a sample, means for mixing the reagents from the reservoirs with the sample, and a viewing area for visual or automated analysis of the sample/reagent mixture.

Deoms et al. differs from present claims 172 and 213 in that it does not describe the following elements of these claims:

Valves or inlet shut-off device: Because Deoms et al. does not describe the use valves or inlet shut-off devices to isolate the sample track, the channel cannot be used as a **sample storage channel**. Further, the

channel of Deoms et al. lacks the **particle capture regions** described and claimed in the present invention.

Because Deoms et al. lacks these elements, it does not anticipate claims 172 and 213 of the present invention.

Mochida (US 5,147,607) generally describes reaction vessels for microassays having within them reaction units. The described invention comprises:

> ... a reaction vessel comprising a body structure having provided therein at least one reaction unit comprising a channel having at least one fluid inlet and at least one reagent-immobilized area in the downstream of all of the at least one fluid inlet. (Column 3, line 22.)

In Mochida, the channel in the reaction unit may be straight, branched, curved, or winding, and may have dimensions that are appropriate for capillary action and movement of fluids. The channel is in fluidic connection with a reservoir which is in fluidic connection with an inlet. The reagent-immobilized area downstream of the inlet is the area in which reactions between the sample and sample-specific binding agents occur and analysis takes place. The channels may have transparent covers to allow analysis of color changes at the reagent-immobilized zone. Mochida also describes the use of a "throat", or narrowing of the channel, to control the rate of fluid flow and prevent counter-flow back towards the inlet, and the use of suction means to remove sample or reagents from the channel.

Mochida differs from present claims 172 and 213 in that it is does not disclose:

Inlet shut-off interfac : There is no mechanism that completely shuts off the inlet from the channel. The described throat does not provide a complete closure.

Valve between the channel and the analysis region: Mochida does not describe any means for isolating the downstream reagent-immobilized area from the main channel.

Because Mochida lacks both an inlet shut-off interface and a valve between the channel and the reagent-immobilized area, the channels described by Mochida cannot be storage chambers. Therefore, Mochida does not anticipate the claims of the present invention.

Altendorf et al. (US 5,726,751) generally describes a "...flow cytometer made of two components: a flow cytometer optical head and a disposable flow module." (Column 1, line 66.) The flow module is micromachined in silicon or other crystalline materials. The channels are V-shaped and may have dimensions that allow for laminar flow of fluids as well as single-file particle flow. The module also has a transparent cover plate for access of the channel to a light source, and collection of reflected light. Altendorf et al. also describe the use of sample inlets and outlets, means for applying pressure to the flow module to aid in sample delivery, and the possible use of a sheath flow for hydrodynamic focusing.

Altendorf et al. differs from present claims 172 and 213 in that it is lacking disclosure of:

Inl t shut-off interface and valving upstream of the analytical r gion: Because Altendorf et al. does not describe any means to isolate the channel between the inlet and the outlet, it cannot be a storage channel.

Convoluted channels: The channels described by Altendorf et al. are straight, and therefore also do not contain **particle capture regions.**

Altendorf et al. therefore does not anticipate claims 172 and 213 of the present invention.

Zanzucchi et al. (US 5,755,942) provides:

> ... a system for processing a plurality of tests or syntheses in parallel comprising a sample channel for moving samples into a microlaboratory array of a plurality of wells connected by one or more channels for the testing or synthesis of samples, a station for housing the array and an optical system comprising at least one light source and at least one light detector for measuring the samples in the array.... (Abstract.)

Zanzucchi et al. further describes reagent wells for reaction and analysis, pumps for moving liquids, and means for mixing contents of a reagent well (using magnetic microspheres), and valves disposed on either side of the reagent wells.

Zanzucchi et al. differs from present claims 172 and 213 in that it is lacking description of:

Inlet and inlet shut-off device

Convoluted storag channel with particl captur regions: The channels of Zanzucchi et al. are not convoluted and do not contain particle capture regions as disclosed in the present invention.

Storage channel: While Zanzucchi et al. describes the use of magnetic ball valves on either side of the reagent wells, the lack of a valve or shut-off device at the opening of the first reagent well to the channel makes it impossible for the channel of Zanzucchi to be used as a storage channel.

Because Zanzucchi et al. lacks these elements, it does not anticipate claims 172 and 213 of the present invention.

Boyd et al. (US 5,919,711) generally describes:

> An analytical cartridge adapted for use in analyzing fluids which contain liquid and solid components. The cartridge includes a plumbing system composed of various wells or chambers which are interconnected by passageways. After introduction into the cartridge, liquid samples are separated and transported to a test well utilizing a sequential application of centrifugal force followed by pressurization of the system.... (Abstract.)

Boyd et al. differs from present claims 172 and 213 in that it is lacking description of:

Inlet and inlet shut-off device

Convoluted storage channel with particle capture regions: The channels of Boyd et al. are not convoluted and do not contain particle capture regions as disclosed in the present invention.

Storage channel: Because Boyd et al. lacks an inlet shut-off interface and any other valving, the channels described by Boyd et al. could not be used to store fluids.

Because Boyd et al. lacks these elements, it does not anticipate claims 172 and 213 of the present invention.

Southgate et al. (US 5,863,502) describes:

> ...a parallel reaction device for conducting reactions therein comprising one or more reaction flow-ways, each such reaction flow-way comprising one or more chambers connected serially by fluid exchange channels, additional fluid exchange channels connecting such reaction channels in parallel, valve means for initiating and impeding the flow of fluids through such fluid exchange channels, and means for moving the flow of fluids into and out of such chambers. (Abstract.)

The device of Southgate et al. further includes an inlet port with an optional septum, waste chambers, an exhaust port, a detection chamber or channel having a transparent wall, and temperature controllers and monitors. Southgate et al., however, differs from present claims 172 and 213 in that it is lacking disclosure of:

Storage channel: The channels of Southgate et al. are not convoluted in nature and do not contain **particle capture regions**. Further, the valves of Southgate et al. are disposed within the device such that they serve to contain the fluid in the chambers and not in the channels.

Because Southgate et al. lacks these elements, it does not anticipate claims 172 and 213 of the present invention.

Bormann et al. (US 5,601,727) generally describes:

> A device and method for processing a biological fluid comprises directing the biological fluid tangentially or parallel to the face of a separation medium in at least

> one serpentine fluid flow channel such that a plasma-rich fluid passes through the separation medium and a plasma-depleted fluid passes tangentially to the surface of the separation medium. (Abstract.)

Bormann et al. describes a separation device in which at least one wall of the channels of the device is permeable to the biological fluid of interest (column 8, lines 3-22) and in which the separated fluid of interest may be collected externally to the device. Bormann et al. also describes the use of pumps to move fluids through the separation channel. Finally, Bormann et al. discloses that "[t]he biological fluid processing system may also include a seal, valve, clamp, transfer leg closure, stopcock, or the like located within or on at least one of the conduits and/or the containers." (column 6, lines 49-52).

Bormann et al. differs from present claims 172 and 213 in that it does not describe the following elements of these claims:

> **Storage channel:** Bormann et al. describes a separation medium with at least one permeable side. Such a device cannot, therefore, be used to store a fluid sample. The present claims specify a non-porous convoluted storage channel.
>
> **Analysis region and analysis channel**: Bormann et al.'s separation device does not provide for any analysis region or **access to detection means**. Any analysis on the fluid collected by the separation device of Bormann et al. takes place after separation and removal of the separated fluid from the device and collection in an external collection bag.

Because Bormann et al. lacks these elements, it does not anticipate claims 172 and 213 of the present invention.

Chem Ili (US 5,288,463) describes a containment device for use in amplifying and detecting nucleic acid materials comprising:

> ...a reaction compartment with reagents for amplifying nucleic acid material, a detection site, flow means allowing fluid flow from the compartment to the site, reagents allowing detection at the site of amplified nucleic acid material, and a waste compartment...all of the compartment, detection site, and reagents being confined within the device by structure that is sealable after sample insertion to prevent leakage.... (Column 1, lines 45-57.)

Chemelli differs from present claims 172 and 213 in that it does not describe the following elements of these claims:

convoluted storage channel with particle capture regions

Chemelli therefore does not anticipate claims 172 and 213 of the present application.

Miyake et al. (U.S. 5,736,100) describes a sample stirrer:

> ...comprising a piezoelectric element which is disposed in non-contacting relationship to the sample and reagent solutions in the reaction vessel and is electrically energized to generate a soundwave which causes a circulating flow of the reagent solution in the reaction vessel whereby the sample and the reagent solution are mixed in a non-invasive manner. (Abstract)

Miyake et al. does not describe a microfluidic analytical cartridge and does not have any of the elements of present claims 172 and 213 except for

resuspension means. Therefore, Miyake et al. does not anticipate claims 172 and 213.

Weigl et al. (WO 97/39338) describes a system for:

> Detecting the presence and/or measuring the presence of analyte particles in a sample stream also comprising larger particles comprising a) a laminar flow channel; b) at least two inlet means in fluid connection with said laminar flow channel for respectively conducting into said laminar flow channel (1) indicator stream, said indicator stream preferably comprising an indicator substance, for example, a pH-sensitive dye, which indicates the presence of said analyte particles by a detectable change in property when contacted with said analyte particles, and (2) said sample stream; c) wherein said laminar flow channel has a depth sufficiently small to allow laminar flow of said streams adjacent to each other and a length sufficient to allow analyte particles to diffuse into said indicator stream to the substantial exclusion of said larger particles in said sample stream to form a detection area; d) outlet means for conducting said streams out of said laminar flow channel to form a single mixed stream. (Claim 1, page 39.)

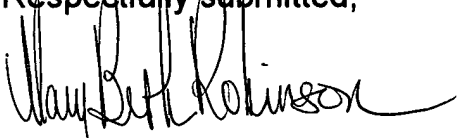
Further, the flow channels of Weigl et al. may be serpentine. However Weigl et al. differs from present claims 172 and 213 in that it does not describe a **storage channel.** Weigl et al. does not disclose the use of valves in the flow channels and therefore the flow channels cannot be used to retain or store fluids. Weigl et al. does not anticipate the present claims 172 and 213.

No *prima facie* case of obviousness can be made out by combining the foregoing references because none of the references teach a need to prevent agglomeration of particles by settling and a need for resuspension of settled

particles. In the absence of such teaching, there would be no motivation for one skilled in the art to combine the features claimed herein.

We have enclosed the required fee under 37 CFR 1.17(i) of $130. If the amount submitted herewith is incorrect, please charge any deficiency or credit any overpayment to Deposit Account No. 07-1969.

Respectfully submitted,



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